IN THE CLAIMS:

The pending claims are listed in the attached:

Appendix A: Pending claims as marked for changes with respect to the issued patent pursuant to 37 CFR §1.173(d).

The only change in the pending claims relative to the last version of record is in claim 12, as follows:

N.E.

12. (Once Amended) A humanized or [chimetic] chimeric human-murine antibody of the monoclonal antibody of claim 9.

Please enter the above-noted change in claim 12.

REMARKS

Reconsideration of the rejections is respectfully requested.

The status of the claims is as follows:

Amended:	12
Cancelled:	None
New:	None
Pending:	1-9, 11-16
Allowed:	1-8

The number of total claims and of independent claims remains the same or less than the amount for which fees were previously paid.

The Applicants respectfully submit that the Amendment meets the requirements of 37 CFR 1.116 since:

A. The Amendment complies with requirements of form expressly set forth in the Office Action by the amendment to claim 12 (the requirement set forth by reference to the Office action dated May 31, 2000).

B. The Amendment places the claims in condition for allowance and in better condition for consideration on appeal.

Accordingly, Applicants respectfully request entry of the Amendment.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Applicants apologize for the oversight whereby the misspelling of "chimeric" in claim 12 was not corrected in the last reply. The misspelling was noted in a rejection set forth in the May 31, 2000 Office action in a rejection under 35 U.S.C. §112, Second Paragraph. This misspelling is corrected with this Amendment and Reply.

Rejections Under 35 U.S.C. §103(a)

It would appear that upon entry of the above-noted correction to claim 12, the only outstanding rejection will be that under 35 U.S.C. §103(a) against claims 9, 11-16, based primarily on Makita, as represented by one or both of a 1992 J. Biol. Chem. article or a 1992 Science article. Applicants' prior response read:

> The Office Action asserts that the claims would have been obvious in view of Makita, as represented by one or both of a 1992 J. Biol. Chem. article or a 1992 Science article, in further view of Harlow, which is text excerpted from a laboratory manual on antibody techniques, or in further view of another article on antibody techniques. Applicants respectfully traverse.
>
> Makita is about polyclonal antibodies. The Office Action links this disclosure to monoclonal antibodies with the following argument:
>
> > ... Harlow et al. teach that hybridomas produce monoclonal antibodies that have homogeneous specificity and affinity for antigen thereby providing an expectation of success [as to binding affinity]...
>
> The above-quoted assertion is a textbook example of borrowing from the applicant's disclosures to make a hindsight reconstruction of the invention.
>
> The above assertion, moreover, is disproved by reference to more germane art. Horiuchi, J. Biol. Chem. 266: 7329-7332, 1991 teaches a *monoclonal* antibody that recognizes AGE-ε-amino-caproic acid. However, as indicated in the attached Declaration of inventor Dr. Henry W. Founds in parent case 08/367,507 (now US Patent 5,744,318), this monoclonal antibody lacks the affinity recited in Applicants claims (and fall short by two orders of magnitude). It clearly was not obvious at the time of the invention that monoclonal antibodies with the recited affinity could be made. Accordingly, Applicants respectfully submit that the rejection must be withdrawn.

To this, the Office responds in part:

> Applicant argues the attached declaration demonstrates that when another researcher made monoclonal antibodies to AGE's that the resulting binding affinity was lower than the presently claimed antibodies.
>
> However, the declaration filed in the Parent case has [not] been received for consideration in the present case.

On the last point raised by the Office in the above text, Applicants respectfully request the Office provide some statutory basis to conclude that a Declaration of an inventor, having the declaratory representations required by 37 CFR §1.68, meeting the signature requirements of 37 CFR §1.4, and timely submitted for its evidentiary weight, has not been received for consideration. Applicants would respectfully submit to the contrary that the Declaration is properly in this record.

The Office further responds to Applicants' prior arguments with the following:

> Furthermore at issue in the present case is whether one of skill in the art at the time of the invention was made would have been motivated to use the above mentioned prior art references to make the claimed monoclonal antibodies with a reasonable expectation of success in creating said antibodies with said affinity in view of what was readily understood by those in the monoclonal antibody screening art to be recognized as undue amount of experimentation to combine the references and arrive at applicant's claimed invention.

As to the elements in the above sentence that recite values relevant under 35 U.S.C. §112, first paragraph, Applicants can only respond that these values implicate a totally separate analysis from the analysis under 35 U.S.C. §103. If the Office intended to maintain an undue experimentation rejection, it was incumbent upon the Office to identify such a rejection in this Office action.

Turning to the values under 35 U.S.C. §103 reflected in the above language, the question is whether one of ordinary skill would have been motivated to make the antibodies that the Applicants made. If the question is whether one would have been motivated to make monoclonal antibodies that recognize AGE-containing components, we can concede for the sake of argument the affirmative. However, the claims call for high affinity with respect to 6-aminocaproic acid browned with glucose. The prior Office action asserts motivation can be found in the recognition in the art that high affinity is desirable since less antibody is required to

perform an assay. But, this asserted motivation does not address why one would choose 6-aminocaproic acid browned with glucose as the selective marker.

Moreover, objective evidence indicates that such motivation clearly did not exist. Horiuchi and coworkers, publishing in a premier journal for biochemical studies, namely the Journal of Biological Chemistry, made monoclonal antibodies to AGE-BSA. The antibody that they chose to highlight in this premier publication, "6D," was in no way represented as in need of improvement. It had perfectly acceptable affinity.[2] Thus, the objective evidence affirms a lack of motivation to find better antibodies with respect to, in particular, 6-aminocaproic acid browned with glucose.

The Declaration of Dr. Founds, in turn, shows that the acceptable for publication in a premier journal monoclonal antibody of Horiuchi was more than two orders of magnitude less effective with respect to 6-aminocaproic acid browned with glucose. Today, given that we have the results of Applicants' work, it is clear that the claimed antibodies can be made without undue experimentation. But, the question under 35 U.S.C. §103 is a reasonable expectation of success in the relevant time frame. Since good monoclonal antibodies fell so short on the binding measure recited in the claims, Applicants respectfully submit that it would have been more than clear, assuming for the sake of argument a motivation, that there would not have been a reasonable expectation of achieving the antibodies claimed.

Accordingly, Applicants respectfully submit that the rejection should be withdrawn.

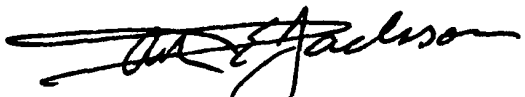
---

[2] According to the authors, the "reactivity of the monoclonal antibody was almost similar to that of the polyclonal antibody; it reacted with AGE-BSA, AGE-HAS, and AGE-Hb but not with their native counterparts." 266 Journal of Biological Chemistry at 7330, column 2.

Conclusion

Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reexamination, reconsideration in view of this response and allowance of the pending claims are earnestly solicited. In light of the above discussion and amendments, Applicants respectfully submit that the claims are in condition for allowance. The issuance of a Notice of Allowance is earnestly solicited.[3]

Respectfully submitted,



Arthur E. Jackson
Registration No. 34,354

Dechert
Princeton Pike Corporate Center
PO Box 5218
Princeton, New Jersey 08543-5218
Allen Bloom (609) 620-3214
Arthur E. Jackson (609) 620-3254
Fax: (609) 620-3259
Attention: Arthur E. Jackson

[3] **FEE DEFICIENCY**

IF ANY ADDITIONAL EXTENSION IS REQUIRED, PLEASE CONSIDER THIS PAPER A PETITION FOR SUCH AN EXTENSION; ANY FEE FOR THE EXTENSION REQUIRED FOR CONSIDERATION OF THIS PAPER BUT NOT ENUMERATED ABOVE OR IN A TRANSMITTAL OR OTHER ASSOCIATED PAPER CAN BE CHARGED TO ACCOUNT NO. 04-0480.

AND/OR

IF ANY ADDITIONAL FEE IS REQUIRED FOR CONSIDERATION OF THIS PAPER, PLEASE CHARGE ACCOUNT NO. 04-0480.

What is claimed is:

1. Monoclonal antibody 4G9 produced by hybridoma 4G9, deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626, or an antigen binding fragment thereof reactive with in vivo produced advanced glycosylation endproducts (AGEs).

2. The monoclonal antibody or antigen binding fragment thereof of claim 1, which specifically binds to serum-AGE proteins, serum-AGE lipids, serum-AGE peptides, LDL-AGE, Hb-AGE, or collagen-AGE.

3. A humanized or chimetic human-murine antibody of the monoclonal antibody of claim 1.

4. The antigen-binding fragment of the monoclonal antibody of claim 1, selected from the group consisting of a single chain Fv fragment, an F(ab') fragment, an F(ab) fragment, and an $F(ab')_2$ fragment.

5. The monoclonal antibody or fragment thereof of claim 1 which is a murine IgG isotype antibody.

6. A labeled antibody wherein the antibody is the antibody of claim 1.

7. A hybridoma deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626.

8. A pharmaceutical composition containing an anti-AGE antibody in combination with a pharmaceutically acceptable carrier; wherein said anti-AGE antibody is the monoclonal antibody in accordance with any of claims 1-3 or 4.

B1

9. A monoclonal antibody, or an antigen binding fragment thereof reactive with in vivo produced advanced glycosylation endproducts (AGEs), wherein the antibody or fragment is selected such that antigen binding measured by binding competition by 6-aminocaproic acid browned with glucose matches that of

a reference binding moiety which is monoclonal antibody 4G9 produced by hybridoma 4G9, deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626 or a fragment thereof corresponding to the antigen binding fragment.

11. The monoclonal antibody or antigen binding fragment thereof of claim 9, which specifically binds to serum-AGE proteins, serum-AGE lipids, serum-AGE peptides, LDL-AGE, Hb-AGE, or collagen-AGE.

B1 cont

12. A humanized or chimeric human-murine antibody of the monoclonal antibody of claim 9.

13. The antigen-binding fragment of the monoclonal antibody of claim 9, selected from the group consisting of a single chain Fv fragment, an F(ab') fragment, an F(ab) fragment, and an $F(ab')_2$ fragment.

14. The monoclonal antibody or fragment thereof of claim 9, which is a murine IgG isotype antibody.

15. A labeled antibody wherein the antibody is the antibody of claim 9.

16. A pharmaceutical composition containing an anti-AGE antibody in combination with a pharmaceutically acceptable carrier; wherein said anti-AGE antibody is the monoclonal antibody in accordance with any of claims 9, 11-12 or 13.